Nutrient-specific feeding and endocrine effects of jejunal infusions in obese animals

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Dailey MJ, Moghadam AA, Moran TH. Nutrient-specific feeding and endocrine effects of jejunal infusions in obese animals. Am J Physiol Regul Integr Comp Physiol 306: R420–R428, 2014. First published January 22, 2014; doi:10.1152/ajpregu.00410.2013.—Intraintestinal nutrient infusions result in variable decreases in food intake and body weight based on the nutrient type and the specific intestinal infusion site. We previously found that intrajejunal infusions of a fatty acid and glucose, but not casein hydrolysate, decreases food intake and body weight in lean chow-fed laboratory rats. To test whether obese, high fat-fed animals would show similar decreases in food intake and body weight in response to intrajejunlal infusions of the same nutrients, equal kilocalorie loads of these nutrients (11.4 kcal) or vehicle were infused into the jejunum of obese, high fat-fed male Sprague-Dawley rats over 7 h/day for 5 consecutive days. Food intake was continuously monitored, and body weight was measured daily. After the infusion on the final day, rats were killed and plasma was collected. Similar to lean chow-fed rats, intrajejunal infusions of linoleic acid (LA) and glucose (Glu), but not casein hydrolysate (Cas), suppressed food intake with no compensatory increase in food intake after the infusion period. In contrast to lean chow-fed rats, only the LA, and not the Glu or Cas, produced decreases in body weight in the obese high-fat-fed rat. There also were no differences in plasma glucagon-like peptide-1 levels in any of the nutrient infusion groups compared with saline infusion. These results suggest that there is a differential response to the same nutrients in lean vs. obese animals.

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Many peptides follow a biological rhythm of peaks and nadirs throughout the day-night cycle [e.g., leptin (36), ghrelin (9), and cortisol (10)], and these rhythms are altered in obese vs. lean individuals (17). These changes are evident as a shift in the rhythm of expression/release or a decrease in the amplitude of expression/release at a particular time point (17). There is even a temporal profile for GLP-1 receptor-mediated hypophagia in rats that is altered by high-fat diet-induced obesity (28). On the basis of these data and the results from experiment 1, we investigated whether there are nutrient-driven changes in the rhythm of GLP-1 in lean vs. obese rats before, during, and after intrajejunual infusion of LA in experiment 2. Results from both experiments may help in understanding differences in lean vs. obese individuals in nutrient sensing.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats (Charles River) were used for both experiments. A total of 48 rats ($n = 16$ per LA, Glu, or Cas experiment with $n = 8$ nutrient infused and $n = 8$ saline infused) were included in experiment 1, and 32 rats ($n = 16$ per lean/chow fed or obese/high-fat fed conditions) were included in experiment 2. In experiment 1, each of the macronutrient infusion and corresponding saline control animals were run separately. In experiment 2, the lean/chow-fed and obese/high-fat fed animals were run together. Animals with an initial weight range of 300–325 g were individually housed and maintained on a 12:12-h light-dark cycle (lights off at 1000). In experiment 1, all rats received ad libitum high-fat diet (Research Diets D12492: 5.24 kcal/g) unless otherwise specified. In experiment 2, half of the rats received ad libitum high-fat diet (Research Diets D12492: 5.24 kcal/g), and half received standard laboratory chow (Global Diet-2018, Harlan Teklad: 3.3 kcal/g) unless otherwise specified. In our experience, it has repeatedly taken 5 wk to see a significant increase in body weight between male Sprague-Dawley rats on a high-fat diet and those on a chow diet, including in experiment 2 in the present study. Thus, 5 wk on the high-fat diet was the used as the time point when nutrient infusions were begun in experiment 1 and experiment 2. Water was available at all times during the experiment. All procedures were approved by the Institutional Animal Care and Use Committee of the Johns Hopkins University.

Jejunal Cannulations

Two days prior to surgery, rats were switched from a high-fat diet or standard chow diet to liquid Ensure (Abbott Laboratories, Abbott Park, IL). For cannula implantations, rats were anesthetized with an intraperitoneal injection of a mixture of ketamine (100 mg/kg) and xylazine (20 mg/kg) at a dose of 1 ml/kg. A laparotomy incision along the ventral midline was made to expose the gastrointestinal tract. A polyurethane catheter (microrenathane 065; Braintree Scientific, Braintree, MA) was inserted into the jejunum. The other end of the catheter was threaded through an opening in the abdominal wall and then passed subcutaneously to an exit on the dorsal surface of the neck. The animals recovered from surgery in their home cage for 5–7 days. They received 2 days of Ensure liquid diet after surgery followed by chow or high-fat diet. Cannula placement and viability were assessed after death by ensuring that the cannula insertion was 50 cm from ileocecal junction and that saline infused into tubing resulted in fluid properly entering the jejunum and traveling toward the distal part of the intestine.

Feeding Tests

After recovery from surgery, the rats were transferred and housed in AccuDiet food intake-monitoring cages (13 in. by 9 in.; Accuscan Instruments, Columbus, OH). A powdered form of the high-fat diet (Research Diets D12492: 5.24 kcal/g) or chow (Global Diet-2018C, Harlan Teklad: 3.3 kcal/g) and water were available ad libitum. Micorenathane tubing (~5 ft in length; MRE-065; Braintree Scientific, Braintree, MA) was connected to the exteriorized catheter of the animal on one end and to syringes on a multisyringe pump at the other end. Rats were able to freely move within the chamber and access the food cups. All rats received jejunal infusions of 0.9% saline [at a range of 0.2 ml/h to 1.73 ml/h depending on the specific nutrient infused (see below) for 7 h beginning at lights out] for 3 days to allow the rats to habituate to the test chamber and infusion cycle. Food intake was continuously monitored by the AccuDiet system for 22 h (2 h with no food access to collect data and to prepare for the next infusion cycle). After the habituation period, the animals were divided into two groups (saline or specific nutrient infusion) based on average body weight and food intake. Half of the rats in each group received jejunal infusions of either 0.9% saline or a nutrient infusion containing a total caloric load of 11.4 kcal for 7 h beginning at lights out. These parameters were chosen on the basis of prior research showing a reduction in food intake over a multiday infusion of an equal caloric load and duration of infusion of linoleic and oleic acid in lean rats (8). Additionally, stopping the infusion with 5 h left in the dark cycle allows us to test whether there could be a compensatory increase in intake after the infusion, while the animals are still in the dark cycle, the period during which the majority of food intake occurs in rats. Because the total load appears to be more effective than the volume of infusion in decreasing food intake (8), the caloric total was held constant across the three infusates used in the present study. In experiment 1, three different nutrients were used and infused into the jejunum for five consecutive days. Caloric concentrations of the solutions differed such that the volumes infused were LA (0.2 ml/h; Sigma-Aldrich, St. Louis, MO), Cas (1.62 ml/h; MP Biomedicals, Solon, OH), or Glu (1.73 ml/h; Sigma-Aldrich) to deliver the total load of 11.4 kcal. In experiment 2, half of the animals received saline, while the other half received LA at the same volume as for experiment 1, and the infusions were administered for 10 consecutive days. For both experiments, food intake was continuously monitored, as described above. Using custom-designed software, food intake data were analyzed to determine meal patterns. Initiation of a “meal” was defined as >200 mg food consumed. The end of each meal was registered when there was >10 min following the end of the last meal.

Plasma Hormone Assays

In experiment 1, rats were decapitated after the last 7-h infusion day, and trunk blood was collected. In experiment 2, four blood samples were collected from each animal at 1000, 1200, 1700, and 2000. Approximately two-hundred microliters of blood was collected via a small tail nick at each time point. Blood was collected from each animal in a random design, so that different animals were sampled on a given day with no more than two blood samples each day with 2 days in between blood sampling days for a given animal. For each experiment, blood from each rat was collected into an EDTA-coated tube and maintained on ice until centrifuged at 3,000 rpm for 10 min. Prior to centrifugation, blood for GLP-1 measurements was treated with 10 μl of DPP-IV inhibitor per milliliter of blood, and blood for PYY was treated with both DPP-IV and 500 KIU of aprotinin. The plasma samples were stored at −80°C until ready to process. The plasma samples from experiment 1 were run in a single assay to determine PYY or GLP-1 to control for interassay variability between the separate macronutrient infusion experiments. A standard radioimmunoassay kit (Millipore, St. Charles, MO) was used to determine plasma PYY (1–36 and 3–36) and was processed according to the manufacturers’ protocol. Plasma GLP-1 (active) was determined using an ELISA kit (Millipore) and was processed according to the manufacturers’ instructions.
Data Analysis

Statistical analysis was only run on data presented within each graph. In experiment 1, food intake and body weight measures were analyzed using separate two-way repeated-measures analyses of variance (ANOVA; 2 × 4; infusion × days) for each nutrient/saline infusate pair with infusate as the between-subject factor and days as the within-subject factor using Number Crunching Statistical Software (NCSS v 2000; Kaysville, UT). Plasma peptide levels were analyzed using a one-way ANOVA for each nutrient/saline infusate pair with infusate as a between-subject factor. In experiment 2, body weight was analyzed using a two-way repeated-measures ANOVA (2 × 9; infusion × days). Food intake measures during infusion, after infusion, and for the dark and light cycles were analyzed using a separate two-way ANOVA (2 × 2; diet × infusate). Plasma GLP-1 levels were analyzed for each diet condition separately using a two-way repeated-measures ANOVA with infusate as the between-subject factor and time as the within-subject factor. The Newman-Keuls method was utilized to test the significance of multiple comparisons of group means when appropriate. Differences among groups were considered statistically significant if \( P < 0.05 \).

RESULTS

Experiment 1

Food intake. Total caloric intake was significantly decreased over the course of infusion days in animals that were infused with LA or Glu, with no change in total caloric intake after Cas infusions (\( P < 0.05 \); Fig. 1). Post hoc tests revealed that jejunal infusions of both LA and Glu significantly decreased the caloric intake on each of the infusion days compared with saline infusions (\( P < 0.05 \); Fig. 1, A and B). This suppression of food intake was significantly greater than the 11.4 kcal of LA infused because the significant decrease in food intake remains, even when the 11.4 kcal are added to the total caloric intake for the LA group for days 4–6 (data not shown). Glu also significantly decreased caloric intake beyond that of the infusate, but only for days 4 and 6 (data not shown).

The decrease in total daily caloric intake in the LA treatment was accounted for by decreases in meal size and meal number (\( P < 0.05 \); data not shown), whereas the decrease in the Glu-infused animals was mainly accounted for by a significant decrease in meal size across infusion days compared with animals infused with saline (\( P < 0.05 \); data not shown). Meal size and number were not affected in Cas-infused animals.

Body weight. The original mean body weight for each of the macronutrient infusion groups at day 1 (see Fig. 2) was as follows: LA = 620 ± 11.5 g, Glu = 624 ± 13.7 g, Cas = 618 ± 15.3 g. LA infusions resulted in significant decreases in body weight compared with saline infusions (\( P < 0.05 \); Fig. 2A). Specifically, significant decreases in body weight on days 6 and 7 were seen for both the LA-treated animals compared with saline-infused animals (\( P < 0.05 \); Fig. 2A). There were no significant differences in body weight for the Glu- or Cas-infused animals compared with the saline-infused animals (Fig. 2, B and C).

Plasma hormones. There were no significant differences in plasma GLP-1 levels between saline and nutrient infusions across the nutrient treatments (Fig. 3). Plasma PYY levels were significantly increased in the LA- and Cas-infused animals compared with the saline-infused controls in each treatment (\( P < 0.05 \); Figs. 4, A and C), with no effect of Glu infusion on PYY levels (Fig. 4B).

Experiment 2

Food intake. Total caloric intake was significantly decreased over the course of infusion days in animals that were infused with LA compared with saline in both the lean/chow-fed and obese/high-fat fed animals (data not shown). Figure 5 repre-

Fig. 1. Daily caloric intake of animals infused with linoleic acid (LA; A), glucose (Glu; B), casein hydrolysate (Cas; C) or saline for each treatment. ○ represents the caloric intake of animals infused with saline in each treatment, ● represents the caloric intake of animals infused with LA, Glu, or Cas. Values are expressed as means ± SE. *\( P < 0.05 \) compared with saline-infused animals.
resents the cumulative hourly intake (averaged across days 4–12 of infusions) for the saline or LA-infused animals in the chow and high-fat groups. These data were further analyzed in bins of time including, food intake during infusion (0–7 h), after infusion (0–24 h), during the dark cycle (0–12 h), and during the light cycle (12–24 h) in each group of animals (Fig. 6).

During the infusion period, LA significantly decreased food intake compared with saline only in the chow-fed animals ($P < 0.05$; Fig. 6A). After the infusion period, though, the animals that had received LA showed a significant decrease in intake only in the high fat-fed group ($P < 0.05$; Fig. 6C). LA infusion caused a significant decrease in intake compared with saline

**Fig. 2.** % change in body weight in animals infused with LA (A), Glu (B), Cas (C), or saline for each treatment. Values are expressed as means ± SE. *$P < 0.05$ compared with saline-infused animals.

**Fig. 3.** Plasma glucagon like peptide-1 (GLP-1) of animals infused with LA (A), Glu (B), Cas (C), or saline for each treatment. Values are expressed as means ± SE.
infusion in both the chow and high-fat groups in the dark cycle (P < 0.05; Fig. 6C), but only in the high-fat group during the light cycle (P < 0.05; Fig. 6D).

**Body weight.** The body weight of the animals fed a high-fat diet was significantly greater than the animals on a chow diet on the last day of saline infusion during the habituation period on day 3 (see Fig. 7; high-fat diet = 619 ± 24.6 g compared with chow = 463 ± 16.5 g). LA infusions resulted in significant decreases in % change of body weight compared with saline infusions in both the lean and obese animals (P < 0.05; Figs. 7, A and B). In the chow-fed animals, LA infusions resulted in a 6% decrease from the original average 463 g for the group, whereas the saline infusion resulted in no change in body weight. In the high-fat fed animals, LA infusions resulted in a 5% decrease from the original average 619 g for the group.

**Plasma hormones.** When the plasma GLP-1 levels were averaged across the four time points assessed, there were no overall differences between the LA and saline-infused animals in either the lean or obese conditions (Fig. 8, A and B). However, jejunal infusions of LA produced a change in the rhythm of GLP-1 across the times assessed in the lean animals (Fig. 8A). There was a decrease in the GLP-1 levels at the 1000 time point (just prior to beginning the 7-h infusion) and an increase at the 1700 time point (at the end of 7-h infusion) when the LA-infused lean animals are compared with the lean saline-infused animals (P < 0.05; Fig. 8A). There were no time-related differences in the obese rats.

**DISCUSSION**

The aim of these experiments was to investigate whether obese rats would show similar changes in food intake, body weight, and plasma satiety signals in response to intrajejunal infusions of specific nutrients to those that were previously seen in lean rats (14). The major findings were 1) intrajejunal infusions of LA and Glu, but not Cas, suppressed food intake

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**Fig. 4.** Plasma peptide YY (PYY) of animals infused with LA (A), Glu (B), Cas (C) or saline for each treatment. Values are expressed as means ± SE. *P < 0.05 compared with saline-infused animals.

**Fig. 5.** Cumulative hourly food intake for animals infused with LA or saline in the chow (A) or high-fat (B) condition. Values indicate the average intake at each hour across the days of the infusion. The times on the x-axis denote the blood-sampling times.
compared with saline-infused animals, 2) plasma GLP-1 levels were not altered in any of the infusion treatments in the obese rats, 3) plasma levels of PYY were increased in the LA- and Cas-infused obese animals, and 4) the rhythm of plasma levels of GLP-1 in lean animals is lost in obese animals.

When the nutrient-driven responses in the obese animals in the present study are compared with previously published responses in lean animals using the same methods (14), we see that jejunal fatty acid and Glu infusions inhibit food intake in both lean and obese animals, with the same lack of response after Cas infusions. LA also is able to decrease body weight in both obese and lean animals. In contrast, Glu infusions decrease body weight only in the lean animals. This may be due to the extent of the decrease in food intake induced by the Glu infusions. In lean animals, Glu infusions are able to decrease food intake ~2–3 times beyond the calories of the infusate, a value much greater than in what we observed in the obese animals. The satiety peptide levels did not always correlate with decreases in food intake in lean or obese animals. LA and Cas infusions resulted in increases in plasma PYY levels in both lean and obese animals, but only intrajejunal LA produced decreases in food intake. Even though Glu produced a decrease in food intake in lean and obese animals, PYY levels were not increased in either nutrient infusion treatment. Thus, plasma PYY levels do not correlate with decreases in food intake using our methods. In contrast to the similar effects of nutrients on PYY in lean and obese animals, there was a differential GLP-1 response between the two groups. In lean animals, GLP-1 levels were increased after LA and Glu infusions, the two treatments that also decreased food intake. Even though these two nutrients produced a decrease in food intake in the obese animals, there was no increase in GLP-1 observed. Even after measuring plasma GLP-1 levels at multiple times before, during, and after the nutrient infusion in experiment 2, there...
still was no increase observed at any time point measured. Taken together, we find that obese and lean animals exhibit the same food intake responses to intrajejunal infusions of nutrients, have the same nutrient-driven PYY response, but a different GLP-1 response.

Both obese and lean animals reduced their food intake in response to intrajejunal infusions of LA and Glu, but only the lean animals showed an increase in plasma GLP-1 levels at the end of the infusion cycle (14). Moreover, blocking the action of the GLP-1 using the GLP-1 receptor antagonist exendin-9 completely attenuates the decrease in food intake after jejunal infusions of LA in lean animals (11). These data suggest a variety of conclusions. First, we know that exendin-9 can have a long-lasting effect on the GLP-1 receptors and, thus, stimulate a greater population of receptors (39). This suggests that exendin-9 may be able to modulate central receptors, while the endogenous intestinally derived GLP-1 may be degraded before it is able to reach the brain. Second, the plasma level of GLP-1 may not be a proper measure of nutrient-driven changes in GLP-1 to affect food intake. Data support a role for local GLP-1 receptors within the intestinal wall in decreasing appetite (for a review, see Ref. 27). LA and Glu may actually increase the release of GLP-1 locally, which can then bind onto receptors located on enteric and sensory neurons to have an effect on food intake (2, 29). This local effect of GLP-1 within the intestine may explain why there is a LA- and Glu-driven decrease in food intake without a correlated increase in plasma GLP-1 levels in the obese animals. It also may explain one mechanism by which the GLP-1 receptor antagonist was able to block this decrease in food intake, by binding onto GLP-1R located within the intestinal wall. Similar effects with CCK, another intestinally derived satiety peptide, have been found. A CCK-A receptor antagonist blocks the feeding suppression due to glucose intestinal infusions even when there is no increase in plasma CCK levels (7). A third explanation could be that local GLP-1 is increased in our obese animals but occurs along with an increase in dipeptidyl peptidase IV (DPP-IV), the pro tease inhibitor known to quickly degrade GLP-1. DPP-IV is produced within the intestine and is increased in rats fed a high-fat diet compared with a standard rodent chow [albeit, these diets differed from those used in the present study (41)] and in obese humans (25). Higher levels of intestinal DPP-IV may then be able to degrade GLP-1 before it reaches systemic circulation and can be measured through our blood sampling. Carr et al. (6), though, suggest that an elevation in plasma DPP-IV activity in obese humans is not the cause of the lower levels of GLP-1 in obese vs. lean individuals. After a mixed meal or oral glucose, plasma levels of total GLP-1 and active GLP-1 are equally reduced in obese subjects. Thus, increased DDP-IV activity in obese individuals would not be the cause. Carr et al. (6) suggest that it is more likely that lower GLP-1 levels reflect a reduction in secretion from the intestine. Even with some of these possible explanations, it still is not clear whether the jejunal nutrients were able to alter behavior in obese animals through gut peptide signaling or through other mechanisms.

Data from humans do not clearly define the relative role of satiety peptides controlling food intake in obese vs. lean individuals but suggest a negative correlation with obesity. Basal GLP-1 concentrations and postprandial GLP-1 release seem to be attenuated in obese compared with lean adults (1, 32). PYY levels also are lower in obese individuals compared with lean (20, 23, 42). In obese children, GLP-1 fasting levels are significantly lower than in lean children and a negative correlation between GLP-1 and body mass index and waist circumference is evident (3). As far as evidence for nutrient-driven changes in satiety hormones in obese individuals, Gibbons et al. (18) found that obese men and women show increases in GLP-1 and PYY after a meal. A high-fat meal will increase GLP-1 and PYY levels to a greater extent than a high-carbohydrate meal. In addition, a rise in GLP-1 after the morning of a high-fat or high-carbohydrate meal is associated with lower-energy intake at a lunch meal. In contrast, PYY was not correlated with the amount of food eaten at the lunch meal. When the effect of weight loss is investigated, weight loss appears to increase postprandial GLP-1 concentrations to a level that is between that of lean and obese individuals (38). Another study, though, showed that postprandial GLP-1 concentrations were significantly lower after weight loss compared with before weight loss levels, even though ratings of satiety were increased and hunger scores decreased (1). After RYGB, patients exhibited a marked increase in postprandial GLP-1 levels as early as 1 wk after surgery, and this marked increase in GLP-1 levels remained increased at 3 mo and 1 y after surgery (30). There are obvious confounds with oral ingestion vs. the method of direct infusion of nutrients into the intestine utilized in the present study. Taken together, though, these data indicate that there are significant differences between lean and obese individuals with respect to hormone release, and that the gut may respond differently to ingested nutrients in obese subjects, compared with lean subjects.

Adam et al. (1) had suggested that the effect of GLP-1 to decrease appetite may be driven by the change in GLP-1

Fig. 8. Plasma GLP-1 of animals infused with LA or saline in the lean, chow-fed condition (A) or obese, high-fat fed condition (B). Values are expressed as means ± SE. *P < 0.05 compared with saline-infused animals.
levels across time. In experiment 2, we see rhythmic changes in GLP-1 during the dark phase of the lean animals, but only a steady GLP-1 level in the obese animals. In addition, the rhythm of plasma GLP-1 is altered in lean animals in response to jejunal infusions of LA. This nutrient-driven change in GLP-1 peaks and nadirs is not apparent in the obese animals. The plateau in GLP-1 rhythm in the obese animals and the shift in rhythm produced by the additional intrajejunal LA infusion were only evident when multiple blood samples were taken. Thus, the variability of results across studies investigating satiety peptide levels may be explained because many studies only sample blood at one time point in a given day. However, this may not be as relevant as seeing whether there is a change in GLP-1 levels before and after a manipulation.

The present results do not differentiate between the effects of obesity and high-fat diet on nutrient-driven changes in ingestive behaviors and satiety signals. One method utilized to try to understand the effect of each of these factors separately is to use two strains of rats that differ in their susceptibility to diet-induced obesity, termed obese-resistant (OR) and obese-prone (OP). Both gastric and duodenal infusion of fats (i.e., Intralipid or sodium linoleate) decreases intake of a high-fat diet to a greater extent in the OR than the OP rats (16, 19). OP, compared with OR, high-energy/high-fat fed rats also have significantly lower plasma GLP-1 levels, decreased protein levels of GLP-1 in the intestinal epithelium, and a reduced number of L cells in the distal ileum (15). Moreover, peripheral administration of a GLP-1 agonist, exendin 4, suppresses high-fat intake to a greater extent in OR than OP rat, indicating greater GLP-1 sensitivity in the OR animals (31). These data suggest that obesity, and not diet, may drive differences in nutrient-driven satiating mechanisms. The caveat with these results is that OP rats eat significantly more of the high-energy/ high-fat diet than the OR. Moreover, the decrease in L cell number, GLP-1 protein expression, and plasma GLP-1 levels in OP rats does not occur when OP rats are fed a chow diet (15). Thus, there appears to be an interaction of obesity with the amount of food or type of food in determining sensitivity to nutrients and satiety mechanisms.

We have examined the effect of jejunal infusion of nutrients in DIO animals as a model of the effect of greater nutrient stimulation in the distal intestine of obese patients that have undergone RYGB. Both the lean and obese animals in our studies decrease food intake after jejunal LA and Glu infusions and decrease body weight after LA, but there is a differential GLP-1 response. This suggests that the decrease in food intake and body weight does not require systemic increases in GLP-1. The increase in GLP-1 levels seen only in our lean animals may be mediated by a nonnutrient-driven mechanism. Indirect GLP-1 stimulation has been documented (13, 33) and can occur through a neuroendocrine loop or through the enteric nervous system (for a review, see Ref. 12). Obesity is known to induce neuroplasticity in autonomic nerves and, thus, our obese rats may have decreased neural mediated GLP-1 secretion. RYGB in DIO rats improves vagal efferent nerve responsiveness to satiety signals (5). This outlines an additional mechanism beyond direct nutrient stimulation by which RYGB may improve satiation.

**Perspectives and Significance**

Even with the many unknown factors and discrepancies among studies, it is clear that there are differences in satiety hormone release and downstream behavioral responses in lean and obese individuals. Greater nutrient delivery to the intestine that occurs with overeating or factors secondary to obesity may alter the morphology and function of intestinal cells. Alterations in the gastrointestinal tract may then lead to greater physiological alterations beyond the digestion and absorption of food. The neural and hormonal connections between the cells of the GI tract and the nervous system play an integral role in affecting metabolism and appetite. If we can understand how nutrients interact with the GI tract to alter cellular morphology and function, we may be able to target segments or cell types along the GI tract through pharmacological manipulation to produce beneficial effects on energy homeostasis.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

Author contributions: M.J.D. and T.H.M. conception and design of research; M.J.D. and A.A.M. performed experiments; M.J.D. and A.A.M. analyzed data; M.J.D. and T.H.M. interpreted results of experiments; M.J.D. prepared figures; M.J.D. drafted manuscript; M.J.D., A.A.M., and T.H.M. edited and revised manuscript; M.J.D., A.A.M., and T.H.M. approved final version of manuscript.

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